PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000358	30.03.2005	30.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07K16/28, C07K16/42, A61K39/395, A61P37/08

Applicant
YISSUM RESEARCH DEVELOPMENT COMPANY ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/000358

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 36-41 (as to IA)

because:

☒ the said international application, or the said claims Nos. 36-41 (as to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-41
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-41
Industrial applicability (IA)	Yes:	Claims	1-35
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 36-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: Ott VL et al. (2000)

D2: WO03064662

D3: WO03030835

2 **Novelty** (Article 33(2) PCT)

2.1 The documents D1-D3 are regarded as being the closest prior art to the subject-matter of independent claims 1,12-14,18,19,26-28,34,36-41.

2.2 D1 reviews the coaggregation of inhibitory receptors (ITIM) e.g. FcγRIIB, gp49 and activating receptors (ITAM) e.g. FcεRI on mast cells as a possible therapeutic target for atopic diseases and allergies (see pg.430 left-hand column 3rd paragraph; "concluding remarks). Coaggregation of gp49 and FcεRI inhibits mast cells activation (see pg.434 right-hand column l.34-37). IL-5 contributes in recruiting eosinophils during allergic reactions (see pg.429 right-hand column l.12-14).

2.3 D2 studies the cross-linking of FcεRI (ITAM) and HM18 (mouse equivalent gp49) or FcγRII (ITIM) with bispecific antibodies to treat allergies (see pg.2 l.20 - pg.4 l.10; ex.2-4).

2.4 D3 teaches also the cross-linking of ITAM and ITIM to treat e.g. asthma. Several ITAM-ITIM combination are suggested (see pg.3 l.10-18; examples).

2.5 None of the available prior art documents however mention a bispecific complex for targeting the ITAM IRp60. Consequently the subject-matter of claims 1-41 appears to be novel (Article 33(2) PCT).

3 **Inventive Step** (Article 33(3) PCT)

3.1 Document D1-D3, are considered to represent the most relevant state of the art, whereby all three documents (see point 2.2-2.4) discloses the concept of cross-linking activating and inhibitory receptors in order to inhibit mast cells activation. D1 moreover also identifies eosinophils to be involved in the allergic response.

3.2 The problem to be solved by the present invention may be regarded as providing a bispecific antibody targeting an alternative ITAM on target cells (mast cells or eosinophils).

3.3 The solution to this problem proposed in claim 1 of the present application, namely to target IRp60, is considered as not involving an inventive step (Article 33(3) PCT) since IRp60 appears to be equivalent to the ITAM chosen in D2 or D3 not leading to any surprising effect or advantages.

3.4 The same is valid, mutatis mutandis for the subject-matter of independent claims 12-14,18,19,26-28,34,36-41, which are therefore also not inventive (Article 33(3) PCT)

3.5 The dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, since they are obvious alternatives for a person skilled in the art in this technical field not leading to any surprising effect.

4 For the assessment of the present claims 36-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

4.1 Claim 1 lacks clarity and is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and examples. Present claim refers to generic "target cells". On one hand this term is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers. thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT. On the other hand the application exemplifies only mast cells and eosinophils and no generalization is envisaged (no support Article 6 PCT).

4.2 The term "bi-specific complex" used throughout the set of claims has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

4.3 The term "homologues thereof" used e.g in claims 1, 12 etc. is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

4.4 The applicant is should check the incorrect dependency in claim 25 (reads 10 to 15 should be 16-20), claim 34 (reads 27 should be 34), claim 38 (reads 1-17 should be 1-15).